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By A. A. Kedrov and A. I. Naumenko

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

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THE ACTION OF CERTAIN PHARMACOLOGICAL AGENTS ON INTRACRANIAL CIRCULATION

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The object of the present research was to investigate the effect on the tonus of the intracranial arteries of various pharmacological substances used clinically in treating headaches. To this end we carried out short-term experiments on 27 cats. /280

In evaluating pharmacological action on the tonus of the intracranial arteries, it should, above all, be borne in mind that this tonus is controlled by a number of factors constantly operating in the organism. The most important of these is the chemical composition of the blood, particularly its carbon dioxide content.

The carbon dioxide level of the blood is the most powerful regulator of the tonus of the intracranial arteries. Another important factor affecting the tonicity of these arteries is the level of central arterial pressure. According to Forbes, Nason and Wortman (1937), Fog (1937, 1938), Klosovskiy (1951), and Kedrov and Naumenko, a drop in central arterial pressure results in a relaxation of the tonus of the intracranial vessels; conversely, an increase in this pressure leads to a reactive intensification of the tonic constriction of the intracranial arteries. Finally, the vasomotor innervation is also known to have a definite influence on the tonus of the intracranial arteries. It has been established that the action of the vasoconstrictor nerves on the vessels of the brain is by no means as powerful as their action on the vessels in other regions of the body (Cobb, 1938, Forbes et al., 1937). Thus, the tonus of the intracranial vessels is, as it were, in a state of floating equilibrium, determined by the totality of the influences enumerated above.

Accordingly, any pharmacological action on the tonus of the

intracranial arteries must be evaluated primarily in terms of the degree in which this equilibrium is disturbed. This is a source of many difficulties in the pharmacological investigation of the intracranial circulation. In order to prove that any substance has a direct pharmacological effect on the tonus of the intracranial arteries, it is necessary to take into account its action on, above all, the respiration and the level of central arterial pressure, or to stabilize these quantities throughout the duration of the experiment, since spontaneous changes in these factors may have an independent effect on the tonus of the intracranial vessels.

EXPERIMENTAL

The experiments were carried out on anesthetized animals (2% medinal solution). We investigated the intracranial circulation by means of electroplethysmography, a method which we have already described in previous articles (Kedrov and Naumenko, 1949, 1951), our only modification, designed to meet possible technical objections, /281 being in the technique of sealing the cranium.

This modification was introduced in connection with the publication of Klosovskiy's research (1951). On the basis of his observations, this author lays great stress on the strictest preservation of hermetic conditions in the cranium, as a necessary condition for the normal circulation of blood through the system of intracranial vessels. According to Klosovskiy, the circulation through the cerebral arteries assumes a pulsating character only if the hermetic conditions normally prevailing in the cranial cavity are disturbed. When these conditions are completely restored, all pulsations in the cerebral arteries disappear. We cannot accept this point of view. Moreover, it is in conflict with much of the published data. Our results enable us to state that the circulation through the intracranial vessels fully preserves its pulsating character even when the continuity of the cranium is restored. Thanks to the presence of cerebrospinal fluid in the cranial cavity, this pulsation is also communicated to the veins carrying blood away from the skull. As a result of the increase in cerebrospinal fluid pressure, each pulse dilation of the arteries "squeezes" blood in the direction of the cranial sinuses. The blood flow in these sinuses is also pulsating. Our observations always confirmed that the outflow of blood from the cranial sinuses is pulsating in character. At the same time, the flow of blood through the capillaries of the brain may remain steady, since the walls of the capillaries are not in contact with cerebro-

spinal fluid, and fluctuations in fluid pressure, due to dilation of the arteries, though communicated to the veins, bypass the cerebral capillaries.

Thus, the pulsation of the blood in the arteries supplying the brain and its membranes not only does not disappear when the blood enters the cranial cavity, as Klosovskiy assumes, but is communicated to the blood flowing through the efferent venous system of the skull. According to our data, there is no fundamental difference between the flow of blood through the intracranial arteries when hermetic conditions are disturbed and the same flow when they are not. The quantitative differences observed apparently depend on the completeness of the compensatory intensification of the outflow of venous blood in response to each pulse dilation of the arteries.

These facts enable us to state that our electroplethysmographic technique will register pulse (and respiratory) dilations of the intracranial arteries and veins, and pulse accelerations in the blood flow through them, even when hermetic conditions are fully preserved.

In this article we shall not have the opportunity to describe in detail the mechanism of the circulation of the blood through the closed cranial cavity. This will be the subject of a separate article.

The cranial defect was closed either by means of the pieces of bone removed during trepanation, as indicated in our previous paper, or by means of special threaded plexiglas plugs, which were screwed tightly into the trepanned opening, after first waxing its edges. In the first case, the surface of the skull in the neighborhood of the defect was covered with a thin layer of collodion, which, in its turn, after careful drying was covered, over a larger area, with a layer of dental cement. When plexiglas plugs were used, the area around them and the points where the electrode leads emerged were also coated with dental cement. On hardening, the latter turned into a stony mass. At the end of each experiment we tested the tightness of the cranial cavity by injecting physiological solution under a pressure of 300 mm Hg.

First, electrodes were introduced into the cranium and inserted between the dura mater and the bone (on each side); others were embedded in the thickness of the brain tissue (Fig. 1). This symmetrical arrangement enabled us, when different pairs of electrodes were connected to the registering apparatus, to investigate the different vascular regions both of the membranes and the substance of the brain itself. In subsequent descriptions of the results of our experiments we shall not distinguish between our investigations of the different vascular regions mentioned, since the reactions of the vessels were in all cases the same.

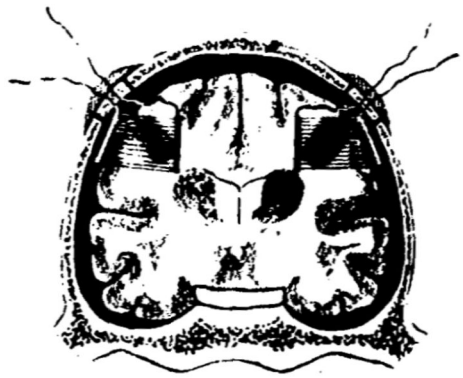

Fig. 1. Schematic of electrode alignment for an intracranial electroplethysmogram.

In investigating the electrical resistance of the intracranial tissues, it is necessary to deal with two kinds of quantities. On the one hand, there is the fundamental resistance of the mass of living tissue. This depends on the properties of the tissue, its colloidal structure, the relative abundance of tissue fluid, the distance between electrodes, the size of the electrodes, the frequency of the current, and a number of other factors. In our studies the fundamental resistance was found to be about 300 ohms. On the other hand, we constantly registered fluctuations in resistance which, as revealed by their shape and periodicity, were connected with the pulse or respiration. The absolute values of these fluctuations were incomparably smaller than the fundamental resistance itself, and (for the pulse waves) did not exceed several hundredths of an ohm. By electroplethysmography we mean the strip-chart recording of the above-mentioned fluctuations in the resistance of the living tissues. In general form, such a curve strongly recalls the curve of an ordinary "mechanical" plethysmogram. In addition to pulse and respiratory fluctuations, the electroplethysmogram shows the upward and downward displacements of the curve corresponding to changes in the blood content of the tissue investigated, and, if the recording strip is made to move sufficiently slowly, so-called third-order waves.

/282

Our previously published results (Kedrov and Naumenko, 1949, 1951; Kedrov and Liberman, 1949) enabled us to connect the above fluctuations in the electrical resistance of the living tissue with changes in the blood content of the vessels in the region investigated and with fluctuations in the rate of blood flow through these vessels.

In analyzing the intracranial electroplethysmograms, we took into account changes in the rhythm and magnitude (amplitude) of the pulse and respiratory spikes, as well as shifts in the general level of the electroplethysmographic curve. Changes in amplitude were treated as follows: the degree of pulse dilation (increase in volume) of an artery is determined by the arterial (pulse) pressure tending to displace the wall of the artery and by the tension in the artery wall tending to resist this displacement. Accordingly, we regarded an increase in the amplitude of the pulse spikes of the electroplethysmogram during an interval of falling or constant central arterial pressure as an indication of a decrease in the tonus of the intracranial arteries. A decrease in the pulse spikes of the electroplethysmogram during an interval of rising or constant central arterial pressure we regarded as an indication of an increase in the tonus of the intracranial arteries.

In these experiments we found it easy to stabilize respiration by using artificial respiration with a constant rhythm and constant volume of the respiratory movements. As far as the arterial pressure is concerned, it was continuously registered, and the level noted each time an intracranial electroplethysmogram was recorded (the pressure was registered by means of a mercury manometer, connected with a cannula, tied into the animal's femoral artery; the record was made on smoked paper).

In the experiments with artificial respiration the animals were curarized. All the pharmacological substances tested were administered intravenously in the doses specified below (on the average one-fourth of the human therapeutic dose). Aqueous solutions were employed and so designed that the total amount of solution introduced did not exceed 0.5-1.0 ml, in order to avoid an increase in pressure due to the introduction into the blood channel of an excessive amount of liquid. It was especially important to avoid introducing excessive amounts of electrolytic solutions, since the latter may cause changes in the conductivity of the blood and tissues, and hence artificial fluctuations in the electroplethysmographic curve.

In our investigations we tried to determine the quantitative as well as the qualitative effects of a given pharmacological agent. /283
We based our comparative evaluation of the action of different chemical agents on the tonus of the intracranial vessels on the action of carbon dioxide. The action of carbon dioxide is distinguished

by its extreme intensity and constancy.

Experiments with carbon dioxide

The carbon dioxide content of the blood was increased as follows. A cannula, tied into the animal's trachea, was connected by means of a rubber tube with a spirometer, previously filled with a definite (6-6.5 l) volume of air. The animal, breathing normally, was forced to inhale and exhale air in a confined space, in which, naturally, the oxygen concentration gradually decreased, while the carbon dioxide concentration correspondingly rose. In order to demonstrate the specific effect of carbon dioxide, the same experiment was repeated in the following modified form: in the path of the air between the tracheotomic cannula and the spirometer we introduced a vessel filled with a saturated solution of barium hydroxide, which absorbs carbon dioxide, so that the animal experienced the effects of anoxia without the accumulation of excess carbon dioxide. In both forms of the experiment, carbon dioxide is observed to exert its greatest influence roughly 10 to 15 minutes after the experiment has begun. After this we disconnected the tracheotomic cannula from the spirometer and the animal was able to breathe normally. The curves corresponding to these experiments are shown in Fig. 2. A comparison of the two curves clearly reveals that when an animal suffers asphyxia under conditions providing for the elimination of carbon dioxide from the air it breathes, the increase in the amplitude of the pulse spikes of the electroplethysmogram is considerably less than when an excess of carbon dioxide accumulates in the animal's blood. It is precisely this latter phenomenon that is /284
connected with the maximum fall in the tonus of the intracranial vessels occurring during asphyxia. It seems to us that the above results confirm our earlier conclusion to the effect that carbon dioxide is a very powerful chemical (pharmacological) agent acting on the tonus of the intracranial arteries. On the other hand, in view of the magnitude of the increase in the pulse waves of the electroplethysmogram at the height of asphyxia, and the subsequent return to the starting value, it appears that the intracranial vessels are in a state of constant tonic constriction, the degree of which is considerable.

When the animal is subjected to asphyxia, there is an important increase in the central arterial pressure. In our view it is impossible to associate the above-mentioned changes in the pulse spikes of the intracranial electroplethysmogram solely with this

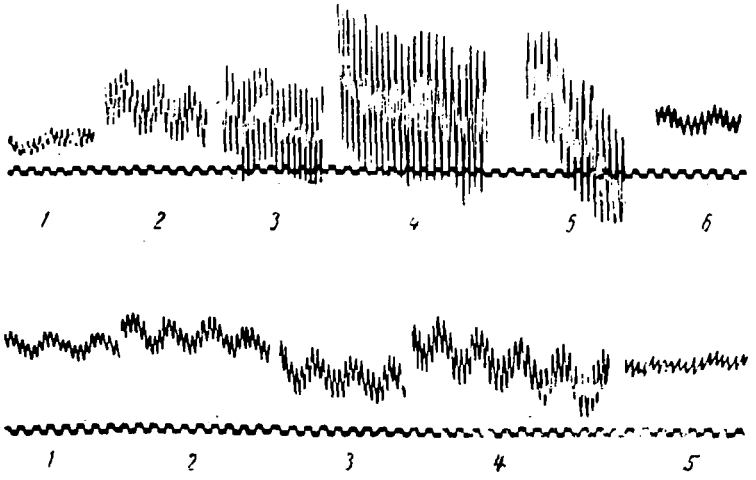

Fig. 2. Intracranial electroplethysmograms in the cat.

The numerals refer to sections of the intracranial plethysmogram corresponding to different experimental conditions.

Upper series: 1 - free respiration; 2 - in limited six-liter volume of air (5th minute of breathing); 3 - same conditions (9th minute of breathing); 4 - same conditions (12th minute of breathing); 5 - free breathing restored (15th minute of experiment); 6 - free breathing (20th minute of experiment).

Lower series: 1 - free breathing; 2 - in limited six-liter volume of air, with the inspired and expired air passing through vessel containing solution of barium hydroxide (5th minute of breathing); 3 - same conditions (9th minute of breathing); 4 - same conditions (12th minute of breathing); 5 - free breathing (20th minute of experiment).

increase in pressure, since even large spontaneous increases in arterial pressure do not cause changes in the intracranial electroplethysmogram to anything like the same extent. Thus, for example, when the abdominal aorta is clamped, the arterial pressure sharply increases (sometimes doubles), while in this case the increase in the amplitude of the pulse spikes of the electroplethysmogram is not more than twofold. During asphyxia, however, this same increase may reach 12 to 15-fold. With respect to sensitivity to the carbon dioxide of the blood, the tonus of the intracranial arteries can be compared only with the respiratory center.

Experiments with caffeine

In clinical practice caffeine has long been used to treat headaches of vascular origin. Its dilative action on the cerebral vessels was established many years ago in various perfusion experiments (Berezin, 1916). The intravenous administration of 0.25 ml of a 10% solution of caffeine and sodium benzoate leads consistently and regularly to the following changes in the intracranial electroplethysmogram (Fig. 3): 30-40 seconds after administration there is a distinct increase in the pulse spikes (roughly threefold). Thereafter, the increased amplitude diminishes slowly, returning to its original value 30-40 minutes after the substance was first administered. The fall in the tonus of the intracranial arteries under the influence of caffeine cannot possibly be linked with the action of caffeine on the arterial pressure, since in these experiments the fall in arterial pressure was comparatively slight. Thus, we can confirm existing notions concerning the direct influence of caffeine preparations on the tonus of the intracranial arteries, which they tend to reduce.

Finesinger (1932) has published data on the differences in the action of caffeine on the vessels of the cerebral membranes of an animal according to the nature of the anesthesia; under amytal anesthesia the effect of caffeine was to dilate the vessels of the cerebral membranes, under ether anesthesia to constrict them. The published data stimulated us to investigate the effect of caffeine on the intracranial vessels of animals under ether anesthesia. However, in these instances we obtained the effect described above, indicating that caffeine has a dilative action on the vessels of the brain.

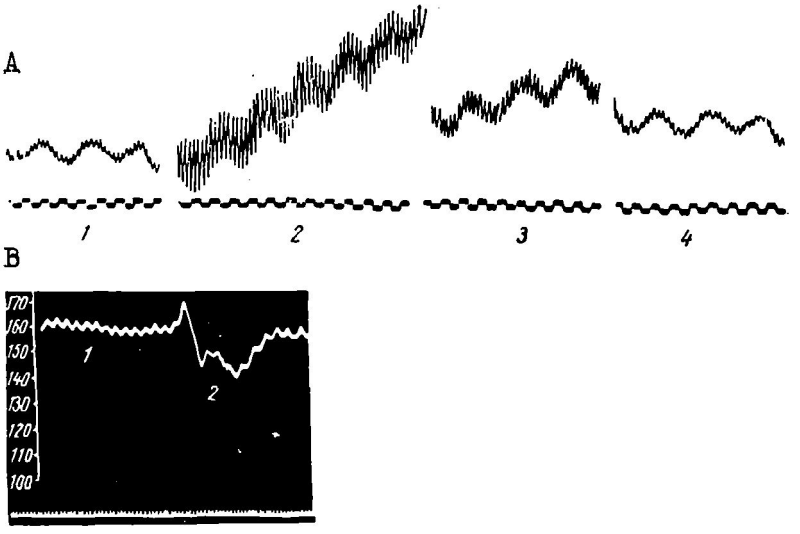

Fig. 3. Record of intracranial electroplethysmogram (A) and arterial pressure (B) in the cat.

The numerals refer to sections of the curves corresponding to different experimental conditions: 1 - before administering caffeine; 2 - immediately after administering caffeine; 3 - 20 min. after administering caffeine; 4 - 40 min. after administering caffeine.

Time mark every 0.5 sec.

Experiments with nitroglycerin

Clinicians occasionally make use of weak solutions of sodium nitrite to treat headaches of vascular origin (nitroglycerin often intensifies head pains). The intravenous administration of one-half of a drop of a 1% alcoholic solution of nitroglycerin (diluted in 1 ml of physiological solution) leads almost instantaneously to a

pronounced drop in arterial pressure. The intracranial electroplethysmogram undergoes important changes, the pulse spikes sharply increasing (three- or fourfold). For two to three minutes the pulse spikes continue high, but then begin to fall, returning to the /285

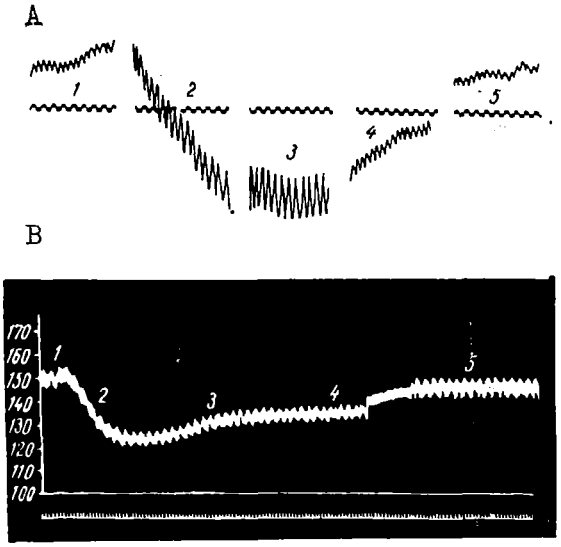

Fig. 4. Record of intracranial electroplethysmogram (A) and arterial pressure (B) in the cat.

The numerals refer to sections of the curves corresponding to different experimental conditions: 1 - before administering nitroglycerin; 2 - immediately after administering nitroglycerin; 3 - 30 sec. after administering nitroglycerin (fall in level of curve continues); 4 - 1 min. after administering nitroglycerin (curve still below normal); 5 - 1.5 min. after administering nitroglycerin.

initial value in five to six minutes. The arterial pressure returns to the starting level before the reverse cycle of the electroplethysmogram is complete. The separate phases of the corresponding changes in the electroplethysmogram are shown in Fig. 4. The problem of the effect of nitrites on the tonus of the intracranial arteries entails the following question: is it possible to regard this effect as being not direct, but oblique, conditioned only by the reaction of the intracranial arteries to a fall in the central pressure resulting from the introduction of the substance in question? In answering this question we shall base ourselves solely on an evaluation of the quantitative aspect of the matter: an unrelated drop in pressure might lead to a certain increase in the pulse spikes of the electroplethysmogram, but the scale of this increase would be less, even if the pressure drop were large.

Experiments with dibazol

Dibazol (2-benzylbenzimidazole hydrochloride) was synthesized, studied and recommended for clinical use by Soviet scientists (Anichkov, Poraykoshits and Lazarev, 1951). The changes in the electroplethysmographic curve following the intravenous administration of 0.5 ml of a 1% solution of dibazol strongly recall, in rapidity of onset and shortness of duration, those observed after the administration of nitroglycerin. There is a distinct increase in the pulse spikes of the electroplethysmogram, but this increase is somewhat less than in the case of nitrites.

Experiments with nicotinic acid, citrin, and citral

Nicotinic acid was proposed as a means of treating headaches by Condorelli (1940), and has since been used in clinical practice. /286
The use of citral for medical purposes was recommended by Balakhovskiy and Budnitskaya (1946); the favorable effect of this preparation on headaches was established by Litvak (1946) and Litvak and Stupina (1950). We repeatedly administered nicotinic acid (vitamin P-P) to animals, intravenously, in doses of from 5 to 50 mg. This substance was not observed to have any marked effect on the tonus of the intracranial vessels. We also tried administering nicotinic acid against a background of slight asphyxia and, inversely, under

conditions of hyperventilation, our idea being that the effect of the preparation might be thrown into relief against a known "predisposition" of the intracranial vessels to dilate or contract. These experiments, too, failed to indicate any activity on the part of

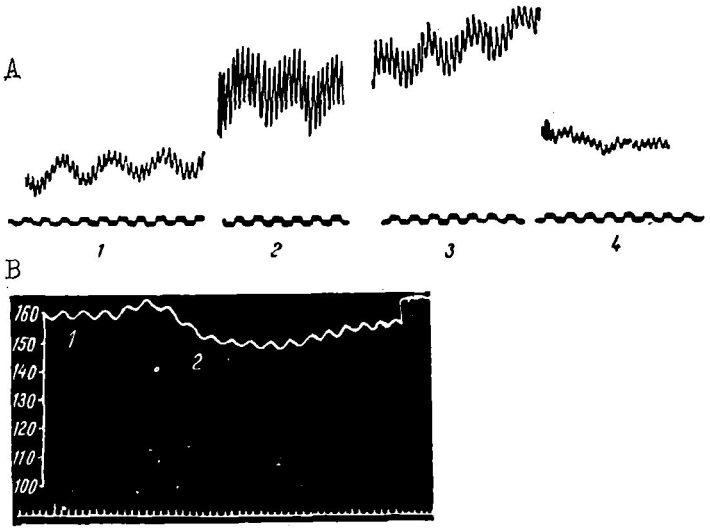

Fig. 5. Record of intracranial electroplethysmogram (A) and arterial pressure (B) in the cat.

The numerals refer to sections of the curves corresponding to different experimental conditions: 1 - before administering dibazol; 2 - immediately after administering dibazol; 3 - 1 min. after administering dibazol; 4 - 5 min. after administering dibazol.

nicotinic acid. Similar results were obtained in relation to the action of citrin on the tonus of the intracranial vessels when

administered in doses of 10, 30, and 50 mg. As far as citral (a derivative of vitamin A) is concerned, in alcoholic solutions it has a distinct effect, consisting in a reduction of the tonus of the intracranial arteries (increase in the amplitude of the pulse spikes of the electroplethysmogram). However, control experiments showed that the 70° alcohol in which the citral was dissolved had a similar effect. As for aqueous solutions of citral, these gave less consistent results, the changes in the spikes of the electroplethysmogram being small and possibly attributable to the drop in arterial pressure connected with the intravenous administration of the citral preparations.

On the basis of a quantitative evaluation of the action of the pharmacological agents mentioned on the tonus of the intracranial arteries we were able to compare their activity with that of carbon dioxide. Actually, carbon dioxide is not a pharmacological agent, since it also serves the organism as a physiological regulator of intracranial circulation, but at the same time it is undoubtedly a very active chemical agent influencing the tonus of the intracranial arteries. In compiling the table presented below, we took as our criterion the extent of the increase in the amplitude of the pulse spikes of the electroplethysmogram as compared with the initial value. Thus, under the influence of carbon dioxide the amplitude of the pulse spikes may increase 12 to 15 times compared with the initial value; accordingly, in the table the action of carbon dioxide on the tonus of the intracranial arteries is indicated by twelve plus signs: /287

Comparative effect of various chemical agents on the tonus of the intracranial arteries (the extent of the reduction in tonus is indicated by the number of plus signs)

Carbon dioxide	++++++++++++
Nitrites (nitroglycerin)	++++
Caffeine	+++
Dibazol	++

[Table cont'd. on next page]

[Table cont'd.]

Citral	+ -
Nicotinic acid	-
Citrin	-
70° alcohol	+

Caffeine has the longest depressant action on the tonus of the intracranial arteries. The effect of the other substances tested wears off considerably sooner. The tabulated data coincide fairly closely with those of Schmidt and Hendrich (cited by Klosovskiy, 1951), relating to changes in the cerebral blood flow in animals under the influence of various pharmacological agents.

Among the general characteristics possessed by all these pharmacological agents, our attention is attracted to the following: as the effect of the substance decreases the spikes of the electroplethysmogram return to their former, initial value. If electroplethysmography is continued, then, as a rule, the pulse spikes of the electroplethysmogram decrease further, falling below the initial value. This "aftereffect" of pharmacological action may be due to the fact that, as a result of the intensification of cerebral circulation attributable to the action of the vasodilator, the products of tissue metabolism and, in particular, carbon dioxide, are intensively washed out, as, for example, in the case of hyperventilation. /288

By comparing the nature of the effect of the pharmacological agents tested on the tonus of the intracranial vessels with their effect on headaches of vascular origin, it is possible to arrive at the following conclusions: pharmacological substances with an especially pronounced depressant action on the tonus of the intracranial arteries (nitroglycerin, carbon dioxide) intensify head pains.

Some of the substances which, according to clinical observations, have a favorable therapeutic effect on headaches of vascular origin (nicotinic acid, citral, citrin) do not have any pronounced effect on the tonus of the intracranial vessels.

In our experiments, caffeine, which has the most consistent therapeutic action in regard to headaches of the type mentioned, had a moderately intense vasodilative effect which later gave way to a certain increase in the tonus of the intracranial arteries.

Taking into account these results, and, moreover, the above-mentioned brevity of the vasodilative effect (reduction in the tonus of the intracranial vessels), which may last a matter of minutes, it seems to us improbable that this vasodilative effect is associated with the analgetic action of the pharmacological agents tested in cases of headaches of vascular origin. Their analgetic action must therefore depend upon another mechanism.

SUMMARY

1. The intracranial arteries are constantly in a state of tonic constriction of considerable intensity.

2. The chemical agent with the most powerful action on the tonus of the intracranial arteries (tending to reduce it) is carbon dioxide.

3. The following pharmacological substances have a direct depressant action on the tonus of the intracranial arteries: nitrites, caffeine, dibazol. Of these caffeine has the longest-lasting effect.

4. Nicotinic acid (vitamin P-P) and citrin (a vitamin of the C group) have no marked effect on the tonus of the intracranial arteries. Citral (a derivative of vitamin A) has a weakly expressed effect on the tonus of the intracranial arteries, tending to reduce it to a slight degree.

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